

**REMARKS****Interview Summary**

Applicants thank the Examiner and practice specialist Debbie Reynolds for the very helpful and courteous interview held Thursday, August 26<sup>th</sup>, 2004, with Dr. Jay Short and Carolyn Erickson (in person), and Gregory Einhorn, Diane Tsuda, Tim Torchia and Calvin Fan (telephonically).

In the Office Communication mailed September 02, 2004, the Examiner provided a summary of the interview (see supplemental sheet, PTOL-413), and asked Applicants to file an additional statement of the substance of the interview. As noted in the Office Communication interview summary, Applicants faxed an RCE Response and Amendment responsive to the Final Office Action mailed April 28, 2004, prior to the interview.

In the interview all pending claims were discussed. Dr. Short, who has served as Chief Technology Officer and Director of the company since its inception, discussed the history and scientific discovery focus of Diversa Corporation, the owner of this application. Diversa Corporation's proprietary methodologies for identifying and genetically engineering (mutating) nucleic acids and polypeptides (e.g., enzymes) were also discussed both for the company's historical context and to address the outstanding section 112, first paragraph, enablement issues for the pending claims. The interview focused on enablement issues, including what was known and routine to one skilled in the art at the time of the invention. The general thrust of Applicants' arguments was that the specification enabled the skilled artisan to make and use the invention because, inter alia, methods for identifying and making the claimed genus of nucleic acids were well known in the art. Applicants discussed many specific examples of methods known in the art at the time of the invention that had been used to routinely make nucleic acids, e.g., a genus of enzyme-encoding polynucleotides, and to screen them for enzymatic, e.g., polymerase, activity without undue experimentation. While Applicants argued that structural descriptions of the claimed nucleic acids for guidance was not necessary to routinely and predictably make the claimed genus of nucleic

acids (because, e.g., of the routine nature of these protocols), they also maintained that sufficient structural guidance was known and available to the skilled artisan. Applicants discussed examples of structural guidance available to the skilled artisan at the time of the invention. It was noted, for example, that knowledge of known polymerase structures and sequences could have been used as guidance to the skilled artisan as to what amino acid substitutions could have been made to make the genus of polymerases of the invention (this supplementary response further addresses this issue, please note remarks, below). Applicants also discussed specific examples of guidance in the specification.

After the Examiner has reviewed this supplementary response and amendment, if the Examiner believes a telephonic interview would help expedite prosecution, please call Applicants' representative at (858) 720-5133.

#### Status of the Claims

##### *Pending claims*

Claims 1 to 17 and 28 to 45 are pending.

##### *Claims canceled and added in the instant amendment*

Claims 46 to 55 are added and claim 8 is canceled, without prejudice. Thus, after entry of the instant amendment, claims 1 to 7, 9 to 12, 16-17 and 28 to 54 will be pending.

Claims 34 to 35 and 38 have been withdrawn. In the instant office action claim 44 is withdrawn, the Patent Office alleging that newly added claim 44 is drawn to an invention that is independent or distinct from the elected invention. Thus, claims 1 to 7, 9 to 12, 16, 17, 28 to 33, 36, 37 and 39 to 55 will be pending and under consideration.

*Outstanding Rejections*

Claims 16 and 17 stand rejected under 35 U.S.C. §112, second paragraph. Claims 4-17 and 39-43, are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification. Claims 1-17, 28-33 and 36-37 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Claims 4-15, 17 and 39-43 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Gelfand, et al., U.S. Patent No. 5,491,086.

Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims; please see Applicants' response of August 25, 2004.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims in this and previous responses. For example, support for claims directed to nucleic acids encoding polypeptides having polymerase activity and having its based on an exemplary nucleic acid, wherein polymerase' sequence has at least one conservative substitution, and in one aspect, the at least one conservative amino acid residue substitution does not occur at an active site of the polymerase, can be found, inter alia, on the paragraph from line 25, page 14, to line 5, page 15. Support for claims directed to nucleic acids encoding polypeptides having polymerase activity and having its sequence based on a percent sequence identity (homology) to an exemplary nucleic acid, except that variation to the exemplary sequence does not occur at an active site of the polymerase, can be found, inter alia, on lines 25 to 30, page 14. Support for claims directed to nucleic acids encoding polymerases having various sequence identities (homologies) to, e.g., fragments, such as active sites, can also be found, inter alia, on page 52, lines 5 to 33. Support for claims directed to nucleic acids encoding polypeptides having polymerase activity and having its sequence based on a percent sequence identity (homology) to an exemplary nucleic acid can also be found, inter alia, on page 42, lines 30 to 34.

Issues under 35 U.S.C. §112, first paragraph

Applicants respectfully request consideration of these remarks as a supplement to Applicants' RCE response of August 25, 2004.

Enablement

Claims 1 to 17, 28 to 33, 36 and 37 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled by the specification such that one skilled in the art to which it pertains could make and/or use the invention commensurate in scope with these claims.

As discussed in Applicants' RCE response of August 25, 2004, the Patent Office remains concerned that because there may be insufficient guidance as to which changes in sequence would be acceptable to retain the desired activity or function, it would be undue experimentation to test (screen for) a large number of variants to determine if a nucleic acid encoded a polymerase and was within the scope of the claimed invention. In that response, Applicants maintained that the specification did provide the skilled artisan a reasonable amount of guidance with respect to screening for polymerases, citing specific examples of guidance from the specification. In that response, Applicants also noted that Dr. Short had declared, inter alia, that the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art, e.g., screening enzymes, and nucleic acids encoding enzymes, for polymerase activity was very high.

Applicants also noted that the specification provided guidance to the skilled artisan as to what amino acid substitutions could have been made to make the genus of polymerases of the invention. Applicants averred that direction to the skilled artisan as to which amino acid residues could have been substituted, deleted or inserted into a nucleic acid of the invention to obtain structural, and functional, homologues of an enzyme of the invention could have been found in the art at the time of the invention, and cited various examples of relevant teachings.

In further support of this point, i.e., that the skilled artisan using the teaching of the specification had sufficient guidance as to what amino acid substitutions could have been made to make the genus of polymerases of the invention (i.e., what nucleotide substitutions could have been made to make the genus of polymerase-encoding nucleic acids of the invention), Applicants respectfully note that if the skilled artisan desired guidance as to which amino acid residues could be modified to obtain structural or functional variants of a polymerase enzyme of the invention (Applicants have maintained that it would not have been necessary for one skilled in the art to understand which specific regions of polymerase structure could be modified to generate the genus of nucleic acids or polypeptides of the invention without undue experimentation), that information was, *inter alia*, readily available in the form of polymerase sequences known in the art at the time of the invention. A routine, simple sequence alignment comparison of known polymerase sequences would have identified regions of identity and dissimilarity to provide guidance to the skilled artisan as to which sequences could be changed, or not changed, to generate structural and/or functional variations of an exemplary polymerase of the invention. As illustrated in the attached sequence alignment (see Exhibit A) of a random selection of polymerases known in the art at the time of the invention (polymerases known prior to August 6<sup>th</sup> 1997), including the exemplary polymerase sequence of the invention (designated 1PY2\_001), regions of common structural identity between polymerases were readily identifiable. The sequence alignment highlights in colors regions of structural identity, with yellow representing regions of common structural identity between the polymerases. As defined by Wang *et al* (1989) FASEB J. 3, 14-21, there are five predicted functional domains: Region I contains two absolutely conserved aspartate residues that are in the catalytic site of all polymerases.

The polymerase sequences used in the Appendix alignment belong to Type B polymerases which are replicative enzymes in Eukaryotes and most likely also Archaea. The first crystal structure of this type of polymerase came from the crystal structure of gp43 from bacteriophage RB69 (June 27<sup>th</sup> 1997, Cell 89:1087-1089). See Appendix A for detailed citations of sources of the aligned polymerases.

Accordingly, while not necessary, but if desired, one skilled in the art at the time of the invention had many sources of guidance, in addition to the specification, to start from a nucleic acid of the invention and determine which amino acid residues could be modified, substituted, deleted or inserted into a sequence to make, identify, screen for and use structural and/or functional variants of an exemplary polymerase of the invention without undue experimentation.

Applicants have also amended selected claims to address the issue of the scope of the claimed genus of nucleic acids. For example, amended claim 1 is directed to nucleic acids comprising a sequence having at least 85% sequence identity to SEQ ID NO:1.

In light of remarks in Applicants' previous responses, and in these supplementary remarks and the instant amendment, Applicants respectfully submit that the pending claims are fully enabled by and sufficiently described in the specification to meet the requirements of 35 U.S.C. §112, first paragraph.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs and 35 U.S.C. §102(b). Applicants respectfully submit that all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants believe that no additional fees are necessitated by the present response and amendment. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 03-1952 referencing docket no. 564462001613. Please credit any overpayment to this account.

After the Examiner has reviewed this supplementary response and amendment, if the Examiner believes a telephonic interview would help expedite prosecution, please call Applicants' representative at (858) 720-5133.

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Respectfully submitted,

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